REMARKS

The March 24, 2003 Official Action has been carefully considered. In view of the amendments submitted herewith and these remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, it is noted that a shortened statutory response period of three (3) months was set in the March 24, 2003 Official Action. Accordingly, the initial response period expired June 24, 2003. A petition for a one (1) month extension of the response period is presented with this Amendment and Request for Reconsideration, which is being filed before the expiration of the one (1) month extension period.

In the March 24, 2003 Official Action, the restriction requirement set forth in the November 5, 2002 Official Action was modified by rejoining on the claims of Groups II and III with Group I, with the result that examination has been carried out with respect to SEQ ID Nos: 1-3, variants, fragments and fusion peptides containing same. The restriction requirement was otherwise still deemed proper and made final. Consequently, Claims 12-19, 22-24, 27-29, 33-35 and 37 have been withdrawn from consideration in this application.

Applicants reiterate that their earlier election in response to the restriction requirement is without prejudice to their right to file one or more continuing applications, as provided in 35 U.S.C. §121, on the subject matter of the withdrawn claims.

The present application has been objected to in several respects in the March 24, 2003 Official Action. Specifically, an objection was raised under 37 C.F.R. §1.821(d) because of the omission of a sequence identifier at page 7, lines 17-18 of the specification. Furthermore, Claims 2, 3, 7 and 9 are deemed objectionable, as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. The Examiner also objected to Claims 1 and 4, as it is allegedly unclear whether these claims recite closed or open language. An Abstract on a separate sheet was also required in the March 24, 2003 Official Action.

Turning to the substantive aspects of the March 24, 2003 Official Action, Claim 5 stands rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out the subject matter which applicants regard as the invention. It is the Examiner's position in this regard that a fragment of the 15 amino acids sequence cannot be equal to the full 15 amino acid sequence.

Claims 2-9, 11, 30-32 and 36 have been rejected under 35 U.S.C. §112, first paragraph, based on allegedly insufficient enablement. In this connection, the Examiner acknowledges that the present specification is enabling for a peptide of SEQ ID NO: 1-3 which is capable of modulating a fibrin fragment E activity, but contends that the specification does not reasonably provide enablement for the variants, fragments and variants of fragments called for in the rejected claims. The Examiner cites a number

of literature references in support of this ground of rejection, which purportedly provide evidence for the proposition that "even a single amino acid substitution or...inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein." The Examiner further contends in this regard that it would take undue trial and error to practice the claimed invention, in view of the quantity of experimentation necessary, the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims. These last-mentioned points of criticism are among the so-called "Wands factors", which are enumerated in In re Wands, 8 U.S.P.Q.2d, 1400, 1404 (Fed. Cir. 1988).

Claims 2-9, 11, 30-32 and 36 have been separately rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to provide a written description of the invention which reasonably conveys to one skilled in the art that the inventors, at the time this application was filed, had possession of the claimed invention. Here again, this rejection is based on the recitations of "variant", "fragment" and "variant of a fragment" in the rejected claims.

Claims 7 and 9 also stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by published International Patent Application WO 98/54208 of Castelhano et al.

The foregoing objections and rejections constitute all of the grounds set forth in the March 24, 2003 Official Action

for refusing the present application.

In accordance with the present amendment, the specification has been amended to provide an appropriate sequence identifier at page 7, lines 17-18.

In addition, an Abstract on a separate sheet is submitted herewith.

As for the present claim amendments, the introduction of Claim 1 has been amended to recite "A peptide composed of an amino acid sequence selected from the group consisting of....". Claim 4 has been amended in the same manner. As a result of these amendments, the objection to Claims 1 and 4 in paragraph 8 of the March 24, 2003 Official Action is believed to be overcome.

Claim 4 also specifies that the peptide is "between 8-14 amino acids in length". Support for this amendment is provided in the present specification at page 6, line 20. Cf. In re Blaser, 194 U.S.P.Q. 122 (CCPA 1977) (disclosure of broad range provides support for narrower included range). In view of this amendment, Claim 5 has been cancelled.

The subject matter of Claims 2 and 3 has been combined and re-presented as independent Claim 38. The recitation in Claim 38 of a peptide "composed of a variant of an amino acid sequence selected from the group consisting of [SEQ ID NOs: 1-3]" is further characterized as "having one or two conservative amino acid substitutions with respect to said amino acid sequence". Support for this amendment is provided in the present

specification at page 7, line 36.

Claims 10, 11, 21, 31, 32 and 36 are unchanged.

Claims 2, 3, 5-9 and 30 are cancelled by this amendment. In view of the cancellation of Claims 2, 3, 5-9 and 30, the various objections and rejections of those claims in the March 24, 2003 Official Action are rendered moot. Applicants wish to make clear, however, that the cancellation of these claims should not be construed as indicative of applicants' concurrence or acquiescence in the various objections and rejections thereof in the March 24, 2003 Official Action, or otherwise as an abandonment of applicants' efforts to secure patent protection on the subject matter of these claims. To the contrary, applicants' vigorously dispute those grounds of objection and rejection. Such arguments as applicants have to advance and rebuttal, however, are being reserved for a continuing application which is expected to include claims directed to the subject matter of one or more of cancelled claims 2, 3, 5-9 and 30.

No new matter has been introduced into this application by reason of any of the amendments presented herewith.

For the reasons set forth below, applicants respectfully submit that the 35 U.S.C. § 112, first paragraph, rejections of Claims 2-9, 11, 30-32 and 36, as set forth in the March 24, 2003 Official Action, either lack merit or cannot be maintained in view of the present amendments. These grounds of rejection are, therefore, respectfully traversed.

A. Claims 4, 10, 11, 31, 32, 36 And 38 (The Latter Corr sponding To Original Claims 2 And 3) Fully Comply With The Enablement Requirement Of 35 U.S.C. §112, First Paragraph

At the outset it should also be noted that in the present case, three different variants **are provided**, i.e. SEQ ID NOs: 1-3. With respect to SEQ ID NOs: 1 and 2, these differ by a single Cys to Ser substitution, which is conservative (see table on page 8, 3rd row). With respect to SEQ ID NOs: 1 and 3, these differ by a single Gly to Val substitution, which is non-conservative (see table on page 8, 3rd row). With respect to SEQ ID NOs: 2 and 3, these differ by the two substitutions above. All of these variants provide the disclosed activity.

In addition to the above-mentioned disclosure of variants embodying this invention, applicants submit that in terms of *making* further variants and fragments, it is clear that this is well within the capabilities of those skilled in the art.

In terms of *the biological activity* of the variants and fragments of this invention, firstly given the narrow genus of variants being claimed , it is submitted that there are no well founded reasons to doubt that such variants will share the biological activity of the recited sequences. Those skilled in the art are well aware that it is the sequence and nature of the amino acid side chains of a peptide that determine its biological activity. Conservative substitutions conserve (by definition) that sequence and nature, and therefore, **it is reasonable to expect** that such substitutions can be made without altering

biological activity. The table on page 8 clearly identifies suitable amino acids which may be substituted conservatively. These are grouped within sub-classes of non-polar, polar-uncharged, polar-charged and aromatic residues.

Secondly, Examples 2 and 4 give sufficient direction as to how to use any peptide variant of this invention, such that the desired effect can be achieved. Applicants do not believe that the claimed activity is unpredictable nor do they accept that undue experimentation is required by those skilled in the art in order to practice the invention as presently claimed.

Applicants also take exception to the Examiner's rote recital of the Wands factors as supporting the position that undue experimentation is required to practice this invention. The presently amended claims cannot be considered unduly broad. Moreover, the level of skill in the field of this invention is quite high. The state of the art is well-developed and the present specification provides working examples and guidance which are more than sufficient to practice the full scope of the claimed invention. In this connection, the Examiner should bear in mind the following observation by the Court in Wands, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988):

> "That *some* experimentation may be required is not fatal; the issue is whether the amount of experimentation required is 'undue'."

Although some experimentation may be necessary in carrying out the present invention, the amount of experimentation involved

certainly cannot be considered excessive or undue in light of the disclosure provided by applicants herein. Therefore, when all of the Wands factors are duly considered, it is beyond question that the claimed invention is fully enabled by the present specification

The Examiner has selected several references from the art which are asserted to support the statement that:

> "...what appears to be an inconsequential chemical modification will often dramatically effect the biological activity..."

Taking these in turn:

(i) Ding et al. investigated Arg to Ala substitutions in the first 55 amino acids of the C-terminal end of FGF. It is applicants' understanding from Figure 3 that each mutant had (at least) **3 or 4** mutations which were **non-conservative** and even then biological activity was **unaffected** for mutants 3 and 4, and **not completely lost** even for mutant 1&2 (**7 non-conservative** substitutions in the region said to be responsible for activity, i.e. the terminal 21 amino acids).

Applicants submit this publication by Ding et al. supports the proposition that it is reasonable to assume that **1 or 2 conservative substitutions** in the recited sequences in the present case should retain activity.

(ii) The Examiner notes that Burgess et al. shows a Lys to Glu substitution, i.e. a +ve to a -ve substitution, which is the **very opposite of a conservative substitution**. Applicants do

not believe that the fact that such a radical change in what was already identified as a key residue has any bearing on the present case.

(iii) With respect to the position 47 substitution disclosed by Lazar et al., which is relied on by the Examiner, this seems to illustrate only that even in potentially important residues, the charge and polarity may not be critical for biological activity (discussion, column 1, 13th-11th line from bottom). With respect to position 48, the authors **did not expect** to see the change which they saw (discussion, column 1, 4th line from bottom). What this illustrates is that generally those skilled in the art **do expect** that conservative substitutions will not have profound effects on activity. The fact that there are **surprising exceptions** sometimes (worthy of note in the scientific press) does not mean that this is not a **reasonable expectation**.

(iv) Kogan et al. confirms that **sometimes** what might be predicted, does not happen (with respect to Glu107Asp in E-selectin). However, applicants again submit that the fact that there are exceptions to the generally accepted rule that conservative substitutions will not profoundly affect activity does not mean that it is not a reasonable rule to follow. Moreover, there is nothing in this reference to suggest the authors were discussing biological effects in general, rather than E-selectin in particular.

Thus, contrary to the examiner's position, applicants do not accept that even this *limited* selection of references concerning amino acid substitutions (from the enormous literature where conservative substitutions do not affect activity) proves that they "**often** dramatically effect" activity. If this was really the case those skilled in the art would not "expect" to see the contrary (cf. Lazar).

Applicants do not agree that Burgess et al. contradicts this view. This reference is seemingly primarily concerned with solvent accessibility, and with substitutions of varying hydrophobicity, rather than conservative substitutions. Indeed the authors state: "An amino acid sequence encodes a message that determines the shape and function of a protein. This message is highly degenerate in that many different sequences can code for proteins with essentially the same structure and activity." (Id at 1306, column 1) and " . . .proteins are surprisingly tolerant of amino acid substitutions . . ." (Id at 1306, column 2) and "[t]he structural information at most surface sites is highly degenerate. Except for functionally important residues, exterior positions seem to be important chiefly in maintaining a reasonably polar surface. The information contained in buried residues is also degenerate, the main requirement that these residues remain hydrophobic." (Id at 1309, column 1). The same reference goes on to explain that the main requirement for structural integrity of a protein is the maintenance of areas of relative hydrophobicity and hydrophilicity and that consequently,

the structure, and therefore function, of a protein is fairly resilient to amino acid substitutions, especially as many such substitutions will be conservative with respect to hydrophobicity."

Therefore, applicants are willing to concede that it is **possible** that some conservative "variants" of the recited sequences **may surprisingly** fall outside the scope of the claim (because they lack the required activity). However, this possibility should not *per se* be justification for asserting that the claimed subject matter is not itself enabled by the specification.

Similarly, it is reasonable to assume that, even though the recited 15 amino acid sequences have demonstrated activity, removal of a small number of amino acids from the N- or C-terminus would not impact upon this.

Regarding the making of any fusion protein comprising any membrane translation sequence, the specification at page 6, line 32 to page 7, line 25 details the second peptide portion of the fusion protein. In particular, page 7, lines 10-19 gives specific examples of a membrane translation sequence, capable of directing a peptide through the membrane of a eukaryotic cell.

In summary, applicants submit that there is, in the Examiner's words "reasonable correlation" between the scope of the present claims, and the invention disclosed in the specification.

For all of the above reasons, the 35 U.S.C. §112, first paragraph rejection of Claims 2-9, 11, 30-32 and 36 based on alleged inadequate enablement is untenable and should be withdrawn.

B. Claims 4,10,11,31,32,36 And 38, As Now Amended, Satisfy The Written Description Requirement of 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 2-9, 11, 30-32 and 36 as failing to satisfy the written description requirement of 35 U.S.C. 112, first paragraph. The alleged deficiencies noted in support of this rejection essentially correspond to those given with respect to the enablement rejection addressed above, and applicants believe that the foregoing remarks are relevant here also.

As discussed above, applicants have explicitly provided a small genus including different types of substitution at different positions and shown that all are active. Applicants believe that this genus is representative of the larger genus encompassed by the amended claims because all members will be closely related (no more than 2 conservative substitutions) and because of the description in the specification of an assay which is effective to identify other members of the genus. On the facts of the present case, those of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus. See attached

extract from "Synopsis Of Application Of Written Description Guidelines".

Additionally, applicants submit that it would be inequitable to insist upon limitation of the claims to only the specified sequences. As stated in *In re Goffe*, 191 USPQ 429 (CCPA 1976):

> "For all practical purposes, the Board would limit Appellant to claims involving the specific materials disclosed in the examples, so that a competitor seeking to avoid infringing the claims would merely have to follow the disclosure in the subsequently issued patent to find a substitute. However, to provide effective incentives, claims must adequately protect inventors. To demand that the first to disclose shall limit his claims to what he has found to work or to materials which meet the guidelines specified for "preferred" materials in a process such as the one herein involved would not serve the constitutional purpose of promoting progress in the useful arts" (Emphasis supplied).

For the foregoing reasons, the rejection of Claims 2-9, 11, 30-32 and 36 for allegedly failing to comply with the written description requirement of 35 U.S.C. §112, first paragraph, is improper and should, therefore, be withdrawn.

In view of the present amendments and the foregoing remarks, it is respectfully requested that the objections and rejections set forth in the March 24, 2003 Official Action be withdrawn and that this application be passed to issue and such action is earnestly solicited.

DANN DORFMAN HERRELL and
SKILLMAN, P.C.

Attorneys for Applicant

By 
Patrick J. Hagan
Registration No. 27,643

PJH:jmn

Enclosure: extract from "Synopsis of Application of Written Description Guidelines"

Ann x II - extract from "SYNOPSIS OF APPLICATION OF WRITTEN DESCRIPTION GUIDELINES"

Example 14: Product by Function

Sp cification: The specification exemplifies a protein isolated from liver that catalyzes the reaction of A B. The isolated protein was sequenced and was determined to have the sequence as set forth in SEQ ID NO: 3. The specification also contemplates but does not exemplify variants of the protein wherein the variant can have any or all of the following: substitutions, deletions, insertions and additions. The specification indicates that procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art and provides an assay for detecting the catalytic activity of the protein.

Claim:
A protein having SEQ ID NO: 3 and variants thereof that are at least 95% identical to SEQ ID NO: 3 and catalyze the reaction of A B.

Analysis:
A review of the full content of the specification indicates that a protein having SEQ ID NO: 3 or variants having 95% identity to SEQ ID NO: 3 and having catalytic activity are essential to the operation of the claimed invention. The procedures for making variants of SEQ ID NO: 3 are conventional in the art and an assay is described which will identify other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO: 3 which have 95% identity to SEQ ID NO: 3 and retain its activity are conventional in the art. A review of the claim indicates that variants of SEQ ID NO: 3 include but are not limited to those variants of SEQ ID NO: 3 with substitutions, deletions, insertions and additions; but all variants must possess the specified catalytic activity and must have at least 95% identity to the SEQ ID NO: 3. Additionally, the claim is drawn to a protein which comprises SEQ ID NO:3 or a variant thereof that has 95% identity to SEQ ID NO: 3. In other words, the protein claimed may be larger than SEQ ID NO: 3 or its variant with 95% identity to SEQ ID NO: 3. It should be noted that "having" is open language, equivalent to "comprising". The claim has two different generic embodiments, the first being a protein which comprises SEQ ID NO: 3 and the second being variants of SEQ ID NO: 3. There is a single species disclosed, that species being SEQ ID NO: 3. A search of the prior art indicates that SEQ ID NO: 3 is novel and

unobvious. There is actual reduction to practice of the single disclosed species. The specification indicates that the genus of proteins that must be variants of SEQ ID NO: 3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95%identity to the reference sequence, SEQ ID NO: 3. The single species disclosed is representative of the genus because all members have at least95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO: 3 which are capable of the specified catalytic activity. One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.

Conclusion: The disclosure meets the requirements of 35 USC §112 first paragraph as providing adequate written description for the claimed invention.